UNILATERAL INHIBITION OF THE RENAL SHWARTZMAN PHENOMENON FOLLOWING INJECTION OF BACTERIAL FILTRATE INTO THE RENAL ARTERY

By ALAN R. MORITZ, M.D., and DAVID WEIR, M.D.

(From the Institute of Pathology, Western Reserve University, and University Hospitals, Cleveland)

(Received for publication, September 8, 1937)

The experimental production of unilateral renal glomerular damage was undertaken in this investigation for the purpose of observing the secondary involutional renal arterial and arteriolar changes which might be expected to follow parenchymatous destruction. The Shwartzman phenomenon was selected as a desirable method for producing such renal glomerular damage on the basis of a report by Shwartzman in 1930 (1). He made the preparatory injection of bacterial filtrate into the renal artery and 24 hours later the reacting dose of filtrate was injected into the ear vein. He stated that "definite lesions resulted in previously prepared organs" but did not indicate the frequency with which the changes could be elicited nor did he describe their nature. Since then, both Apitz (2, 3) and Gerber (4) have reported the production of a bilateral Shwartzman reaction in the kidneys of rabbits following two or more intravenous (ear vein) injections of bacterial filtrate. Neither investigator reported the elicitation of a unilateral renal reaction. Since, in the present investigation, the production of a unilateral rather than bilateral renal damage was preferred, it was decided to employ Shwartzman's original method of direct intra-renal-arterial injection rather than repeated systemic intravenous injections of the filtrates.

Method

10 rabbits were operated upon under ether anesthesia and the left renal artery of each was exposed by an incision just below and parallel to the lowest rib. The artery was separated from the vein and nerve and was freed of fat. A heavy suture was passed under it to secure traction. The artery was stretched by means

of the thread and varying amounts (Table I) of bacterial filtrate[1] were injected into it, using a 22 gauge needle, having a long bevel. The terminal 3 mm. of the needle was bent at right angles to the shaft. There was frequently no bleeding and rarely more than a few drops of blood were lost after withdrawal of the needle. If the needle passed through both walls of the artery or if there was any leak of the injection fluid because of improper entry of the artery, the animal was discarded. 24 hours later each animal received an intravenous (ear vein) injection of 2 cc. of the same filtrate. 8 of the rabbits died within 23 hours. The other 2 were sacrificed[2] 24 and 28 hours, respectively, after the injection of the reacting factor.

RESULTS

As indicated in Table I, infarction[3] occurred in the left kidney of 3 of the 10. Severe tubular degeneration was seen in one. In no rabbits were the changes of the typical renal Shwartzman reaction observed in the injected kidneys. An entirely unexpected finding was the occurrence of typical renal Shwartzman reactions in the uninjected

[1] The bacterial filtrate was prepared from a culture of *B. aertrycke* obtained through the kindness of Dr. E. E. Ecker. This filtrate was prepared from the surface growth on nutrient agar medium in Kolle flasks. At the end of 24 hours' growth bacteria were scraped from the surface, suspended in sterile distilled water, broken up by shaking with glass beads, and passed through a Seitz filter. The filtrate was potent as a reacting factor in amounts as low as 0.05 cc. 8 of 11 rabbits tested by the intracutaneous injection of 0.1 cc. of the filtrate gave strongly positive Shwartzman reactions in the skin at the site of injection within 6 hours after the subsequent (24 hours) injection of an intravenous reacting dose of 2 cc. of the same filtrate.

[2] All rabbits were killed by injecting between 20 and 30 cc. of air into the ear vein.

[3] Complete or partial infarction was readily distinguished from the disseminated hyaline glomerular thrombosis seen in the positive Shwartzman reaction. The infarcts were obviously older lesions than the Shwartzman reactions and were represented by massive coagulation necrosis with peripheral hemorrhage and leucocytic infiltration. That the infarcts resulted from renal arterial thrombosis due to the injection of the preparatory factor was indicated by the results in a control series of 12 animals. In all of these 0.5 cc. of bacterial filtrate was injected into the left renal artery. In the first 6 the vein and artery were occluded for 15 minutes during and following the injection and in the second 6 no circulatory stasis was deliberately induced. The intravenous injection of reacting factor was not made. Infarcts were seen in the injected kidneys of 2 of the first group and in 1 of the second group, 48 hours after the injection. No changes were observed in the uninjected right kidneys of these animals.

TABLE I

Rabbit No.	Preparatory injection Left renal artery	Provocative injection Ear vein 24 hrs. later	Survival Time after provocative injection		Shwartzman reaction in		
			Died	Sacrificed	Left kidney	Right kidney	Other organs
	cc.	*cc. per kg.*	*hrs.*	*hrs.*			
5-08	0.05	1.00	16		−	+	Not examined
5-13	0.05	0.75		28	(Infarction)	−	" "
5-18	0.06	0.75	23		−	+	" "
5-21	0.06	0.80	4		−	+	" "
5-20	0.06	0.90		24	−	+	" "
5-19	0.06	0.90	10		−	+	" "
27-89	0.10	1.00	5		−	+	−
27-86	0.40	1.00	16		(Infarction)	−	−
27-95	0.60	1.50	3		−	−	−
27-99	0.80	1.50	3		(Infarction)	−	−

TABLE II

Renal Artery and Vein Occluded for 15 Minutes during and after Injection of Filtrate

Rabbit No.	Preparatory injection Left renal artery	Provocative injection Ear vein 24 hrs. later	Survival Time after provocative injection		Shwartzman reaction in		
			Died	Sacrificed	Left kidney	Right kidney	Other organs
	cc.	*cc. per kg.*	*hrs.*	*hrs.*			
27-71	0.10	1.00		24	(Infarction)	+	+
27-68	0.10	1.00		24	(Infarction)	+	+
28-51	0.20	1.00		24	−	+	+
26-39	0.60	1.00		24	−	+	+
26-42	0.80	1.00		23	(Infarction)	−	+
29-76	0.80	1.00		24	−	+	+
29-77	0.80	1.00		24	(Glomerular thrombosis)	−	−
29-78	0.80	1.00	1		(Infarction)	−	−
29-79	0.80	1.60		46	−	−	+
29-81	0.80	1.00		24	−	+	+
29-84	0.80	1.00		23	−	−	+
29-86	0.80	2.00		24	−	−	−
29-89	0.80	1.00	3		−	−	−
30-00	0.80	1.00	1		−	−	−

right kidney of 6 rabbits. The reactions in the right kidneys were similar in all respects to those described in detail by Gerber (4) and were represented by hyaline thrombosis of glomerular capillaries with hemorrhagic necrosis of the tufts and frequently of adjacent convoluted tubules.

The explanation of the refractory state of the injected left kidneys in rabbits obviously susceptible to the Shwartzman reaction as indicated by the occurrence of reactions in the uninjected right kidney of 5 of the 10 rabbits was not apparent. It was thought that the vulnerability of the injected kidney might be increased by retaining the injected bacterial filtrate within the kidney for several minutes.

To accomplish this, 14 animals (Table II) were operated upon and the left kidney was exposed in the same manner as reported in the preceding experiment. Varying amounts of bacterial filtrate were injected in the left renal arteries and during and after the injection circulatory stasis in the kidneys was produced by continued traction on the suture which in these rabbits included both vein and artery. Blood flow through the kidney was stopped for a total period of 15 minutes. 24 hours later these rabbits were injected intravenously (ear vein) with bacterial filtrate and animals were sacrificed at the intervals indicated in Table II. Infarction of the left kidney was seen in 4 rabbits. In one, there was hyaline glomerular thrombosis, not associated, however, with hemorrhage or necrosis and not representative of a typical renal Shwartzman reaction. In the uninjected right kidney of 6 of the 14 rabbits, the typical renal Shwartzman reaction was observed.

Despite the retention of the bacterial filtrate in the left kidney for 15 minutes, the injected kidneys remained refractory and were not rendered susceptible to the reacting injection of the filtrate. As in the preceding experiment, the only renal Shwartzman reactions produced were contralateral in relation to the side injected.

One possible explanation of this persistent refractory state of the injected left kidneys was that a vascular spasm had developed and persisted in the left kidney as a result of the intra-arterial injection of bacterial filtrate, so that the subsequent intravenously injected filtrate (reacting factor) did not reach the kidney in amounts great enough to elicit a Shwartzman reaction.

To investigate this possibility, the right kidney was removed from 10 rabbits (Table III). The rabbits were then placed in metabolism cages for 2 days and the daily amount of urine excreted was measured. During the first 24 hours the urinary output varied between 0 and 85 cc. per animal, and during the second

24 hours between 0 and 175 cc. On the 3rd postoperative day the left renal artery was exposed and injected with 0.2 cc. of bacterial filtrate without occlusion of the vein and artery after the injection. The rabbits were returned to metabolism cages and the urine was collected for the next 24 hours. One animal excreted between 2 and 3 cc. of bloody urine and one excreted none. The other 8 excreted between 10 and 150 cc. 24 hours after the intra-renal-arterial injection of preparatory factor; the 8 survivors received an intravenous injection of bacterial filtrate. One died within 1 hour and 2 died about 4 hours after the injection. The other 6 were killed at the end of 24 hours. The urine output of these 6 ranged between 10 and 250 cc. for the 24 hours following the injection of the reacting factor.

TABLE III

Right Kidney of Each Animal Removed at Beginning of First Day of Experiment

Rabbit No.	Amount of urine		Preparatory injection Left renal artery	Amount of urine	Provocative injection Ear vein 24 hrs. later	Survival Time after provocative injection		Amount of urine	Shwartzman reaction in	
	1st day	2nd day		3rd day		Died	Sacrificed	4th day	Left kidney	Other organs
	cc.	*cc.*	*cc.*	*cc.*	*cc. per kg.*	*hrs.*	*hrs.*	*cc.*		
28-60	85	160	0.50	25	1.00		24	140	−	+
28-16	55	75	0.50	10	1.00		24	70	−	+
28-73	0	0	0.50	0	(Dead)				(Infarction)	−
21-90	0	5	0.50	3	1.00	1		0	−	−
39-91	15	60	0.50	35	1.00	4		0	−	−
39-93	80	95	0.50	150	1.00		24	125	−	+
28-57	10	175	0.50	80	1.00		24	250	−	−
28-58	25	90	0.50	65	1.00		24	10	−	+
28-59	0	25	0.50	30	1.00	4		5	(Infarction)	−
28-60	15	95	0.50	20	1.00		24	40	−	−

As indicated in Table III, none of the animals showed a positive Shwartzman reaction in the injected kidney, although in 4 of them the finding of thrombosis and petechiae in lungs, liver, spleen, and suprarenals indicated that the animals were susceptible to the Shwartzman reaction. Although the kidney of each was refractory, an otherwise generalized reaction had occurred. The injected left kidneys were not rendered vulnerable and did not react despite the fact that the circulation of blood through 3 of the 4 kidneys was adequate to provide for as great an output of urine as was seen in the same animal before injection. This experiment indicated that whatever the nature of the refractory state of the injected kidney might be, it was not due to

vascular spasm with resulting protection against the circulating filtrate of the reacting factor. Neither was the refractory state of the kidney due to a generalized refractory state of the animal inasmuch as the manifestations of a generalized Shwartzman reaction were present in 4 of the animals.

SUMMARY

A positive Shwartzman reaction, as indicated by thrombosis and focal hemorrhage in one or more organs, was elicited in 19 of 34 rabbits in which the preparatory injection of bacterial filtrate was made into the left renal artery and the reacting injection was made in the ear vein 24 hours later. In 24 of the 34 rabbits the kidneys were undisturbed throughout the duration of the experiment except for the intra-arterial injection of the left. In 12 of these 24 a positive Shwartzman reaction was observed in the uninjected right kidneys. In only 1 of the 24 injected left kidneys were there changes that might be construed as representing a positive Shwartzman reaction. The changes in this kidney consisted of glomerular thrombosis, not associated with hemorrhage or necrosis. The positive renal Shwartzman reactions seen in the right kidneys were similar to those reported by Apitz and Gerber as representing the renal changes occurring as part of a generalized Shwartzman reaction. The retention of the bacterial filtrate of the preparatory injection in the left kidney, by obstructing both vein and artery for 15 minutes, did not lessen the refractory state. The removal of the right kidney prior to the experiment, with the subsequent demonstration that circulation through the remaining left kidney was not impaired by the intra-arterial injection of filtrate, indicated that the refractory state of the injected kidney was not the result of failure of the reacting dose of filtrate to reach the kidney. In the unilaterally nephrectomized rabbits the development of a positive reaction in other organs indicated that the lack of reaction in the kidney represented a local refractory state. No explanation of the phenomenon was disclosed by these experiments.

BIBLIOGRAPHY

1. Shwartzman, G., *J. Exp. Med.*, 1930, **51**, 571.
2. Apitz, K., *Virchows Arch. path. Anat.*, 1934, **293**, 1.
3. Apitz, K., *J. Immunol.*, 1935, **29**, 255.
4. Gerber, I. E., *Arch. Path.*, 1936, **21**, 776.